REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-22 remain in this application. Claims 4 and 22 have been withdrawn.

The Examiner has withdrawn claim 22 from further consideration as being drawn to a nonelected species. Claim 4 was withdrawn pursuant to a previous restriction requirement. As claim 1 is a generic claim which fully embraces a method including the compound specified in claim 22, if claim 1 is found to be allowable, claim 22 should no longer be withdrawn. Therefore, it is not proper to require cancellation of these claims.

The Examiner has rejected claims 1, 5-15 and 17-20 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,851,527 to Hansen. This ground of rejection is respectfully traversed.

Claim 1 recites a method for the in-vivo localization of water-insoluble molecules within a solid tumor, which comprises "the administration of a water-soluble prodrug molecule to an animal; said prodrug being a substrate to said enzyme and hydrolyzed by said enzyme molecules present within the tumor, said hydrolysis forming a water-insoluble drug precipitate molecule, wherein said precipitate is trapped within the extracellular space of the solid tumor.

Hansen discloses injecting a mammal with an enzyme-antibody conjugate and thereafter injecting the mammal with a soluble substrate-agent conjugate which is capable of transformation by the enzyme to form a product comprising the agent, which accumulates at the target site for treatment and/or diagnosis. Hansen discloses that "the free drug would . . . be rendered significantly less soluble in the interstitial fluid, and would tend to deposit on the cell membrane of surrounding cells" (column 7, lines 50-54) and "[t]he agent molecules are bound to the polymer in such a way that cleavage by the enzyme will liberate the agent, free of polymer units or bound to a small enough number of units to have the requisite lower solubility, or more favorable partition coefficient to cells, tissues, lesion, lesion components or the like loci at the target site, relative to the fluid bathing such loci" (column 8, lines 18-24). Further, Hansen states that "[c]onversion of a relatively poorly soluble drug to a more soluble drug . . . will improve its solubility in the aqueous phase of serum" (column 7, lines 33-38). (See also column 13, lines 30-33 (conjugate becomes less soluble). Hansen does not teach or suggest the agent, once cleaved

from the substrate-agent conjugate, forms a water-insoluble precipitate or that such agent would be trapped within the extracellular space. In fact, none of the agents taught by Hansen would form a precipitate once they are cleaved and none of the agents taught by Hansen are water-insoluble or would be trapped in the extracellular space, but rather would be capable of permeating a cell membrane. Therefore, claim 1 should be allowable over Hansen. As claims 5-15 and 17-20 depend from claim 1, they should be allowable for the same reason.

Claims 1, 5-15 and 20 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6, 361,774 to Griffiths et al. This ground of rejection is also traversed.

Griffiths et al. disclose a method for increasing the target-specific toxicity of a drug by pretargeting an enzyme to a mammalian target site, and then administering a cytotoxic drug or a prodrug form thereof which is converted to the drug in situ. The drug is detoxified to form an intermediate of lower toxicity and the mammal's ordinary metabolic processes reconverts the detoxified intermediate to its more toxic form by the pretargeted enzyme, thus enhancing its cytotoxicity at the target site. Specifically, Griffiths et al. is concerned with a method for increasing the target-specific toxicity of a chemotherapy drug, i.e., one that must enter a cell to be effective. As with Hansen (which Griffiths et al. reference as a source of examples for substrate-agent conjugates), nowhere is there a teaching or suggestion in Griffiths et al. of a water-insoluble precipitate or any agent that is trapped within the extracellular space of a solid tumor. Again, each of the agents listed are water-soluble and are in no way trapped in the extracellular space. Therefore, this ground of rejection should be withdrawn.

Claims 1-3 and 5-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen in view of U.S. Patent No. 4,975,278 to Senter et al., U.S. Patent No. 6,495,553 to Shepard and further in view of U.S. Patent No. 6,265,427 to Camden, U.S. Patent No. 6,156,739 to Griffin et al., and U.S. Patent No. 5,854,968 to Horwitz et al. This ground of rejection is also traversed.

Senter et al. disclose a method for delivering cytotoxic drugs to tumor cells by the administration of a tumor-specific antibody-enzyme conjugate and the additional administration of a prodrug that is converted at the tumor site, in the presence of the antibody-bound enzyme, to an active cytotoxic drug. Senter et al. fail to cure the deficiency of Hansen with respect to teaching or suggesting the limitation of the formation of a water-insoluble precipitate wherein

such precipitate is trapped within the extracellular space of the solid tumor. Senter et al., rather teach the opposite, stating that the "drug is . . . activated extracellularly and can diffuse into all of the tumor cells at that site."

Shepard discloses methods and examples of molecules for selectively killing a pathological cell by contacting the cell with a prodrug that is a selective substrate for an endogenous, intracellular enzyme. The prodrug is subsequently converted to a cellular toxin. The agents disclosed by Shepard are chemotherapeutic agents which are necessarily internalized in the cell and thus cannot be trapped within the extracellular space of a solid tumor as required by claim 1. Further the agents disclosed by Shepard are not water-insoluble and do not form a precipitate outside the cells. Therefore, Shepard fails to cure the deficiency of Hansen or Griffiths et al.

Camden also fails to cure the deficiency of Hansen and Griffiths et al. with respect to the formation of a water-insoluble precipitate or the entrapment of such precipitate in the extracellular space of a solid tumor. Camden discloses a chemotherapeutic method of treating leukemia using a specific compound or a prodrug form of such compound. There is no teaching or suggestion of a water-insoluble precipitate that is trapped in the extracellular space of a solid tumor.

Griffin et al. also fails to cure the deficiency of Hansen and Griffiths et al. with respect to precipitate that is trapped in the extracellular space of a solid tumor. Griffin et al. disclose quinazolinone compounds which inhibit PARP activity. These compounds necessarily go into the cells as PARP is intracellular. (See, e.g., column 1, lines 34-41, which states "[t]he above-mentioned quinazolinone compounds have been considered to be of interest as promising therapeutic agents for use in conjunction with cytotoxic drugs or radiotherapy, for example in antitumour treatment, because their PARP inhibiting activity can enable them to interfere with intracellular DNA repair mechanisms and thereby potentiate or enhance the effectiveness of such cytotoxic drugs in chemotherapy, or of radiation in radiotherapy.") Griffin et al. do not teach or suggest that these compounds precipitate or that they are trapped in the extracellular space of a tumor. Therefore, as none of the cited references, whether alone or in combination, teach or suggest each of the limitations of independent claim 1, this claim should be allowable. As claims 2-3 and 5-20 depend from claim 1, they should be allowable for the same reason.

In addition, the Examiner has rejected claims 1, 5-15, and 20-21 as being unpatentable over Hansen and Griffiths et al. in view of Griffin et al., U.S. Patent No. 4,107,285 to Christenson and U.S. Patent No. 5,756,502 to Padia. This ground of rejection is respectfully traversed.

Christenson discloses an improved radiolabelled derivative of a methaqualone analog used in the practice of a radioimmunoassay. Christenson fails to cure the deficiency of Hansen, Griffiths et al. and Griffin with respect to a teaching or a suggestion of a water-insoluble precipitate that is trapped within the extracellular space of a solid tumor, as required by independent claim 1.

Padia teaches quinazolinone derivatives useful for suppressing appetite, reducing gastric acid secretion, and the like. As with Christenson, there is no teaching or suggestion whatsoever in Padia of a water-insoluble precipitate that is trapped within the extracellular space of a solid tumor. Therefore, as none of these cited references, whether alone or in combination, teach or suggest each of the limitations of independent claim 1, this claim should be allowable. As claims 5-15 and 20-21 depend from claim 1, they should be allowable for the same reason

In view of the foregoing amendments and remarks, Applicant submits that this application is in condition for allowance. Early notification to that effect is respectfully requested.

The Assistant Commissioner for Patents is hereby authorized to charge any additional fees or credit any excess payment that may be associated with this communication to deposit account **04-1679.**

Respectfully submitted,

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